

Risk Factors for Multidrug-resistant Tuberculosis

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In 2015, 10.4 million people developed tuberculosis (TB) and 580,000 amongst them suffered from multidrug-resistant TB (MDR-TB). From those 580,000 cases of MDR-TB, only 125,000 were detected and reported.¹ A total of 111,000 people began to receive MDR-TB treatment in 2014 while 190,000 MDR-TB patients were estimated to have died, largely due to lack of access to effective treatment.² The mechanism of drug resistance can be caused by genetic factors, factors related to previous treatment and other factors such as comorbidity with diabetes mellitus.^{3,4} Although there is some evidence which postulate host genetic predisposition is the basis for the development of MDR-TB, changes in the genomic content is the major underlying event in the emergence of variants strains in the *M. tuberculosis* complex. Spontaneous chromosomally-borne mutation occurring in *M. tuberculosis* at predictable rates are thought to confer resistance to anti-TB drugs.³ Factors related to previous anti-tuberculosis treatments consists of incomplete or inadequate treatment and also poor treatment adherence. A review of the published literature strongly suggest that the most powerful predictor for the presence of MDR-TB is a history of TB treatment. Many new cases of MDR-TB are created by physician's errors related to drugs regimen, dosing interval and duration of treatment. Multidrug-resistance TB developed due to error in TB management in the past such as initiation of an inadequate regimen using first line anti-TB drugs, the addition of single drug to a failing regimen, the

failure to identify pre-existing resistance and variations in bioavailability of anti-TB drugs that predispose the patient to the development of MDR-TB. Non-adherence to prescribed treatment is often underestimated by physicians and difficult to predict.³⁻⁸ Certain factors such as psychiatric illness, alcoholism, drug addiction and homelessness can predict non-adherence to treatment. Poor compliance with the treatment is also an important factor in the development of acquired drug resistance.³

Diabetes mellitus has been a well-known risk factor for TB in the past. The global convergence of the accelerating type 2 DM pandemic, high TB prevalence and drug-resistant TB during the past couple of decades has become a serious challenge to clinicians worldwide. Over the past few years, some studies have shown that the treatment failure rate is higher in TB patients with DM as comorbidity. Moreover, there is significant association between DM and MDR-TB.^{4,9} There is higher chance of TB bacilli persistence to be present in sputum of pulmonary TB patient with DM than TB-only patient after 5 months treatment, and this persistence made it necessary for more longer treatment. Presence of DM in TB patients cause a longer period for sputum conversion, therefore it may become a major cause of poor treatment outcome in TB patients. Previous studies showed that a major mechanism for the emergence of drugs resistance in TB bacilli is random mutation in the bacterial genome and the pressure of selection by anti-TB drugs. Pulmonary TB in diabetic patients usually

show higher mycobacterial loads at the initiation of treatment, hence they may have higher chance of bacillary mutation and the emergence of MDR-TB with the presenting of higher bacterial loads, longer treatment is needed to clear the bacteria. Therefore, it is not surprising that a higher chance of MDR-TB patients could be found in those patients.⁹ A pharmacokinetic study noted that plasma levels of rifampicin were 53% lower in TB patients with diabetes, which might affect treatment outcomes.¹⁰ Inadequate immune responses of the host may also be important in this negative effect of diabetes. Depressed production of IFN- γ in diabetic patients is related to decreasing immune response to TB infection. Reduction of IL-12 response to mycobacterial stimulation in leukocytes from TB with diabetic patients suggest a compromise of innate immune response.⁹

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